Title: Incubation periods under various anti-retroviral therapies in homogeneous mixing and age-structured dynamical models: A theoretical approach.

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Abstract. We consider previously well-known models in epidemiology where the parameter for incubation period is used as one of the important components to explain the dynamics of the variables. Such models are extended here to explain the dynamics with respect to a given therapy that prolongs the incubation period. A deconvolution method is demonstrated for estimation of parameters in the situations when no-therapy and multiple therapies are given to the infected population. The models and deconvolution method are extended in order to study the impact of therapy in age-structured populations. A generalisation for a situation when $n-$types of therapies are available is given.

Key words: Epidemic models, deconvolution, conditional probability.

1. Preliminaries, basic model and modified models

The incubation period is generally defined as 'the time duration between the time a virus or bacteria enters the human body and the time at which clinical clinical symptoms occur'. This duration can vary from case to case depending upon the route through which the virus or bacteria enters the immune system of an individual and in some cases depends upon the age of the infected individual. For influenza this duration is 1 - 2 days, for common cold 2 - 5 days, for measles 8 - 12 days, for SARS a maximum of up to 10 days, for rubella 14 - 21 days, and for HIV infection to AIDS 6 months to 10 years or more. The incubation period can be used as a measure of rapidity of the illness after interaction with the virus or bacteria. It is not easy to collect information on the incubation period of infected individuals unless they are monitored. One of the direct ways of estimating the average incubation period of a given virus in the population is by surveillance and followup of the infected individuals until they develop symptoms. All the infected individuals may not be aware of their infection until symptoms appear and followup is subject to the availability of an individual. It might not be possible to follow up individuals in a typical situation, where time taken for the onset of symptoms from the infection is longer, especially if infected individuals are lost to followup. Hence, there are limitations on directly estimating the everage incubation period from prospective cohort studies. Nevertheless, the incubation period occupies an important role along with other parameters in modelling the disease spread and understanding the basic reproductive rate. A useful description of various epidemic models, and of estimation of parameters like the incubation period, transmission rates, forces of infections are presented in Anderson and May (1991). The degree of importance of obtaining accurate average incubation periods varies with the incubation period of the disease. This degree of variation causes mathematical models to act sensitively in predicting future burden. Models describing dynamics of disease spread where the incubation period is shorter are less subject for producing misleading results than models for the spread with longer and varying incubation periods. Especially for predicting AIDS, the epidemic models developed, depend heavily on parameters that determine transmission rates of infection from infected to susceptible and on the parameter which explains the average time to progress to AIDS. A review of various modeling approaches and quantitative techniques to estimate the incubation period can be found in Castillo-Chavez (1989) and Brookmeyer and Gail (1994). A set of parametric and non-parametric models are proposed to estimate the incubation period when the data is doubly-censored (Rao et al 2005). The introduction of anti-retroviral therapies and protease inhibitors during the 1990s in several parts of the world resulted decline in opportunistic infections related to AIDS (Mouton et al (1997) et al (1999), Conti, S et al

(2000), Hung et al (2003)). As a result of such interventions, the incubation period was prolonged. There have been attempts to estimate the incubation period that vary due to drug intervention using statistical density functions (Artzrouni (1994)). The impact of this variation on the HIV dynamics, stability and on basic reproduction number has been investigated (Castillo-Chavez et al (1989)). In this section, we first consider a simple ODE model that explains the dynamics of HIV spread in a population leading to AIDS. We then consider a similar model where incubation period is a variable with respect to a given therapy. We address issues of estimating incubation period to be used in such dynamical models and the impact of above mentioned therapies. Various ideas and the outline of this work are given at the end of this section.

Perhaps the most fundamental model for the epidemiology of AIDS is that given by Anderson and May (1988, 1991), which takes the form

$$\begin{aligned} \frac{dX}{dt} &= \Lambda - (\lambda + \mu)\, X, \\ \frac{dY}{dt} &= \lambda X - (d + \mu)\, Y, \\ \frac{dD_z}{dt} &= dY - \gamma D_z. \end{aligned} \tag{1.1}$$

Here the total population (N) is divided into susceptibles (X), infectives (Y) and individuals with the full blown disease (D_z). The parameter Λ is the input into the susceptible class, which can be defined as the number of births in the population, λ is the force of infection, μ is general (non-AIDS related) mortality, γ is disease related mortality and $1/d$ is the average incubation period. Here the incubation period is defined as the duration of time between infection and onset of full blown disease.

There has been an observed increase in the mean incubation period since the availability of therapies for AIDS (UNAIDS, 2002). Drugs are available which cannot eliminate virus from the body, but are helpful in prolonging the life of an individual by slowing the disease progression (in other words increasing the incubation period). For example, Protease inhibitors (say *drug 1)* facilitate in producing non-infectious virus (only infectious virus participates in new virus production), hence slowing the disease progression; anti-retroviral therapy (*say drug 2)* blocks virus from interracting with the non-infected cells and hence reduces the infection process within the cell population (see section 5, Nowak and May (2000) and Perelson and Nelson (1999) for fuller details); and a combination of the above two drugs (*say drug 3*) can be more effective by simultaneously combining the function of *drug 1* and *drug 2.* Note that, when model (1.1) was developed, the above described drugs were not available. We assume that once individuals start taking drugs, their average incubation

period is prolonged. So, instead of assuming a constant $1/d$, we assume that it varies based on the drug type. Thus we define $1/d_i = \int_{\mathbb{R}} z_i g(z_i) dz_i$, for $i = 0, 1, 2, 3$, where $i = 0$ denotes the without drug scenario, $i = 1$ for *drug 1*, $i = 2$ for *drug 2* and $i = 3$ for *drug 3*. Here g is the probability density function with a certain parameter set (say $\mathbf{B}$) and z_i is a continuous random variable representing the incubation period. Here z_i is a real valued function defined on a standard probability space $(S, \mathbb{A}, P)$, where S is the space of elementary events, $\mathbb{A}$ is called a Borel fields, and $P(\mathbb{A})$ is probability of the event $A \in \mathbb{A}$. So, $z : S \to \mathbb{R}$. We can also denote this integral as a Stieltjes integral $\int_{\mathbb{R}} z_i dG(z_i)$, where $G(z) = P(Z < z)$. We further assume without loss of generality that

$$
\begin{aligned}
\int_{\mathbb{R}} z_0 dG(z_0) &< \int_{\mathbb{R}} z_1 dG(z_1) \leq z_2 dG(z_2) < \int_{\mathbb{R}} z_3 dG(z_3), \\
\int_{\mathbb{R}} z_0 dG(z_0) &< \int_{\mathbb{R}} z_1 dG(z_1) > \int_{\mathbb{R}} z_2 dG(z_2) < \int_{\mathbb{R}} z_3 dG(z_3).
\end{aligned} \tag{1.2}
$$

(In the next section, we will give a detailed estimation procedure for $\mathbf{B}$.) Applying these varying incubation periods, model (1.1) is modified as follows:

$$
\begin{aligned}
\frac{dX}{dt} &= \Lambda - (\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3 + \mu) X, \\
\frac{dY_0}{dt} &= \lambda_0 X - \left\{ \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} + \mu \right\} Y_0, \\
\frac{dY_1}{dt} &= \lambda_1 X - \left\{ \left(\int_{\mathbb{R}} z_1 dG(z_1) \right)^{-1} + \mu \right\} Y_1, \\
\frac{dY_2}{dt} &= \lambda_2 X - \left\{ \left(\int_{\mathbb{R}} z_2 dG(z_2) \right)^{-1} + \mu \right\} Y_2, \\
\frac{dY_3}{dt} &= \lambda_3 X - \left\{ \left(\int_{\mathbb{R}} z_3 dG(z_3) \right)^{-1} + \mu \right\} Y_3, \\
\frac{dD_{z_0}}{dt} &= \left(\int_{\mathbb{R}} z_0 dG(z_0) \right)^{-1} Y_0 - \gamma_0 D_{z_0}, \\
\frac{dD_{z_1}}{dt} &= \left(\int_{\mathbb{R}} z_1 dG(z_1) \right)^{-1} Y_1 - \gamma_1 D_{z_1}, \\
\frac{dD_{z_2}}{dt} &= \left(\int_{\mathbb{R}} z_2 dF(z_2) \right)^{-1} Y_2 - \gamma_2 D_{z_2}, \\
\frac{dD_{z_3}}{dt} &= \left(\int_{\mathbb{R}} z_3 dG(z_3) \right)^{-1} Y_3 - \gamma_3 D_{z_3},
\end{aligned}
\tag{1.3}
$$

where Y_0, Y_1, Y_2 and Y_3 are variables for infectives, $D_{z_0}, D_{z_1}, D_{z_2}$ and D_{z_3} are variables for individuals with the full blown disease, $\lambda_0, \lambda_1, \lambda_2$ and $\lambda_3$and $\gamma_0, \gamma_1, \gamma_2$ and γ_3 are variables for disease related mortality for no-drug, *drug 1, drug 2* and *drug 3* respectively. General mortality and disease-related mortality are incorporated in to the model to demonstrate the basic structure of the model, and our aim here is to estimate $\mathbf{B}$ and thus to estimate $\int_{\mathbb{R}} z_i dG(z_i)$ for all i such that simulations of the model are performed. In model (1.3), the total population $N = X + Y_0 + Y_1 + Y_2 + Y_3 + D_{z_0} + D_{z_1} + D_{z_2} + D_{z_3}$ satisfies

$$
\frac{dN}{dt} = \Lambda - \mu X + \mu \sum_{i=0}^{i=3} Y_i - \sum_{i=0}^{3} \gamma_i D_{z_i}.
$$

Estimation of parameters for the varying incubation periods is important for understanding the impact of drugs in prolonging the onset of disease and thus to prolong the life. The set $\mathbf{B}$ will also be useful in obtaining varying basic reproductive rates, R_{0i} for all $i = 0, 1, 2, 3$. This can be computed as

$R_{0i} = \lambda\gamma_i \int_{\mathbb{R}} z_i dG(z_i)$ by assuming independence of the impact of various drugs. So far, there is no evidence that β, the probability of infecting a susceptible partner, changes with the activation of a drug in the body. If we assume this as a constant, then $R_{00} \geq R_{01} \geq$ or $< R_{02} \geq R_{03}$. $R_{01} < \{R_{01}, R_{02}, R_{03}\}$, because individuals are assumed to have longer incubation period due to the effect of drugs. In the absence of clinical evidence, we assume that the impact of *drug1* and *drug2* follows any one of the following relations: $\int_{\mathbb{R}} z_1 dG(z_1) \leq$ or $> \int_{\mathbb{R}} z_2 dG(z_2)$. Similarly, another important epidemiological measure, the doubling time, t_{di} is obtained as $t_{di} = \ln(2) \int_{\mathbb{R}} z_i dG(z_i) / [R_{0i} - 1]$.

Anti-retroviral therapy helps in blocking the virus from interacting with cells and simultaneously providing protease inhibitors helps in producing non-infectious virus. So without loss of generality, it is assumed that the impact of double drug therapy is better than a single drug therapy. If we assume disease related mortality is constant for all i then $\gamma_i = \gamma$. Where there are n types of drugs available, we write the general form for the above dynamical model as follows:

$$
\begin{aligned}
\frac{dX}{dt} &= \Lambda - \left(\sum_{I=0}^{n} \lambda_i + \mu\right) X, \\
\frac{dY_0}{dt} &= \lambda_0 X - \left\{\left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} + \mu\right\} Y_0, \\
&\vdots \quad \vdots \\
\frac{dY_n}{dt} &= \lambda_n X - \left\{\left(\int_{\mathbb{R}} z_n dG(z_n)\right)^{-1} + \mu\right\} Y_n, \\
\frac{dD_{z_0}}{dt} &= \left(\int_{\mathbb{R}} z_0 dG(z_0)\right)^{-1} Y_0 - \gamma_0 D_{z_0}, \\
&\vdots \quad \vdots \\
\frac{dD_{z_n}}{dt} &= \left(\int_{\mathbb{R}} z_n dG(z_n)\right)^{-1} Y_n - \gamma_n D_{z_n},
\end{aligned}
\tag{1.4}
$$

As a special case we can consider all the parameters in the above model as Stieltjes integrals and can estimate them using the rigorous procedure explained in the next section.

This paper is organised as follows: In section 2, we describe in detail the estimation of the set $\mathbf{B}$ for up to three drugs; section 3 gives the corresponding expressions for the conditional probabilities of $N-$drugs. We construct some theoretical examples in section 4 to demonstrate the method explained in section 2. There were several attempts to study, through ODE models, the role of anti-retroviral therapy and protease inhibitors in controlling the virus multiplication inside the human body. In section 5 we briefly review these models. In section 6 analysis for age-structured populations is described in detail. Overall conclusions are given in section 7. Appendix I gives equations for conditinal probability when incubation period for various drug types does not have the monotonicity property. Appendix II gives some more theoretical examples when the incubation period is truncated to the right.

2. Varying incubation periods and conditional probabilities

In this section, we will give a detailed procedure to estimate $\mathbf{B}$ through a deconvolution technique. Let $\mathbf{B}$ be split into a collection of four parameter sets say, $\mathbf{B}=\{B_0, B_1, B_2, B_3\}$ for the four types of scenarios described in the previous section. Let H be the time of infection and Z be the incubation period, then the time of onset of the disease can be represented as $D = H + Z$. There have been studies (see for list of references Brookmeyer and Gail (1994)), in which H and Z were assumed independent and D was estimated through convolution. We outline the general idea of convolution and then give the convolution of H and Z. Suppose (a_n) and (b_n) are two sequences of numbers over the time period, then

$$(a_n) * (b_n) \quad = \quad \sum_{k=0}^{n} a_n b_{n-k} \tag{2.1}$$

where $(a_n) * (b_n)$ is the convolution of these sequences with an operator $'*'$. Suppose a and b are mutually independent random variables and let $A_{\mathcal{L}}(x)$ and $B_{\mathcal{L}}(x)$ be their Laplace transformations, then $a+b$ has the Laplace transformation $A_{\mathcal{L}}B_{\mathcal{L}}$. Since the multiplication of the Laplace transformation is associative and commutative, it follows that $(a_n) * (b_n)$ is also associative and commutative. Instead of discrete notation, suppose a and b are continuous and independent with probability density functions h and g, then the density of $h + g$ is given by

$$f(s) \quad = \quad \int_{-\infty}^{\infty} h(t-s)g(t)dt = \int_{-\infty}^{\infty} h(t)g(t-s)ds$$

.

Suppose $G(s) = \int_{-\infty}^{s} g(s)ds$, and $F(s) = \int_{-\infty}^{s} f(s)ds$ then

$$F(s) = \int_{-\infty}^{\infty} h(t)G(t-s)ds. \tag{2.2}$$

We call F the convolution of h and G. Suppose the above h and G represent the infection density and incubation period distribution function; then the convolution of h and G represents the cumulative number of disease cases reported (or observed), and is given by

$$h * G = \int_{-\infty}^{\infty} h(t)G(t-s)ds. \tag{2.3}$$

The kind of convolution in (2.3) was used to estimate the number of AIDS cases for the first time by Brookmeyer and Gail (1988). Information on G may not be available for some populations. In such situations, G has been estimated through deconvolution from the information available on $h * G$ and h (Rao and Kakehashi, 2004, 2005). In this section we will construct conditional probabilities for each *drug type* and express the function that maximizes $\mathbf{B}$. These kind of conditional probabilities derived for the *drug type* were not available earlier for the incubation periods when the total number of reported disease cases were considered. Note that $h * G$ is the cumulative number of disease cases.

Let $X_0, X_1, X_2, ..., X_{n-k}, ..., X_{n-l}, ..., X_{n-m}, ..., X_n$ be the disease cases available in the time intervals $[U_{i-1}, U_i)$ for $i = 0, 1, 2, ...n-k, ...n-l, ...(n-m)+1, ...n+1$. Suppose $\mathbf{E}$ is the event of diagnosis of disease after the first infection at T_0. Let $\mathbf{E} = \{E_0, E_1, E_2, E_3\}$ and E_0 occurs in the interval $[U_0, U_{n-k})$, E_1 (or E_2) in $[U_{n-k}, U_{n-l})$ (or $[U_{n-l}, U_{n-m})$) and E_3 in $[U_{n-m}, U_n)$. Now D, the cumulative number of disease cases up to time U_n, can be expressed from (2.3) as follows:

$$\begin{aligned} D\left(U_0 \le s \le U_n\right) &= \int_0^{U_{n-k}} h(t)G(t-s)ds + \int_{U_{n-k}}^{U_{n-l}} h(t)G(t-s)ds \\ &\quad + \int_{U_{n-l}}^{U_{n-m}} h(t)G(t-s)ds + \int_{U_{n-m}}^{U_n} h(t)G(t-s)ds, \end{aligned} \tag{2.4}$$

$$\begin{aligned} D\left(\mathbf{A}, \mathbf{B}/U_n\right) &= \textstyle\int_0^{U_{n-k}} h(t/A_0)G(t-s/B_0)ds + \int_{U_{n-k}}^{U_{n-l}} h(t/A_1)G(t-s/B_1)ds \\ &\quad + \textstyle\int_{U_{n-l}}^{U_{n-m}} h(t/A_2)G(t-s/B_2)ds + \int_{U_{n-m}}^{U_n} h(t/A_3)G(t-s/B_3)ds. \end{aligned}$$

In the above equation A_0,A_1, A_2 and A_3 are the parameter sets for the h for $drug0$, $drug1$, $drug2$ and $drug3$. An infected individual could fall in to any of the intervals described above, and similarly a full-blown disease diagnosed individual could fall in the same interval, but for a given individual the chronological time of infection would be earlier than that of diagnosis of the disease. U_{n-k} is the time of introduction of *drugs* after infection at U_0. Individuals who were diagnosed on or after U_{n-k}, and before U_n, were taking one of the three *drugs*. If $E_1 \in [U_{n-k}, U_{n-l})$ and $E_2 \in [U_{n-l}, U_{n-m})$ $Z_1 < Z_2$, otherwise if $E_1 \in [U_{n-l}, U_{n-m})$ and $E_2 \in [U_{n-k}, U_{n-l})$ then and if $E_1, E_2 \in [U_{n-k}, U_{n-m})$ then $Z_1 = Z_2$. An individual who was diagnosed with the disease before U_n must have developed symptoms in one of the four intervals $[U_0, U_{n-k})$, $[U_{n-k}, U_{n-l})$, $[U_{n-l}, U_{n-m})$ and $[U_{n-m}, U_n)$. Let $E_j \in [U_{j-1}, U_j) \subseteq [U_0, U_{n-k})$, then the conditional probability of the occurence of E_j given E is expressed as

$$\begin{aligned} P\left(E_j/E\right) &= P\left(U_{j-1} \leq D \leq U_j / D \leq U_n\right) \\ &= \frac{D\left(A_0, B_0/U_j\right) - D\left(A_0, B_0/U_{j-1}\right)}{D\left(A_0, B_0/U_n\right)} \\ &= \int_0^{U_j} h(t/A_0)G(t-s/B_0)ds. \left[\int_0^{U_n} h(t/A_0)G(t-s/B_0)ds\right]^{-1} \\ &\quad - \int_0^{U_{j-1}} h(t/A_0)G(t-s/B_0)ds. \left[\int_0^{U_n} h(t/A_0)G(t-s/B_0)ds\right]^{-1}. \end{aligned} \tag{2.5}$$

If *drugs* were initiated at U_{n-k}, then these conditional probabilities constructed above will change according to the occurence of E_1, E_2, E_3. Consider $E_1 \cap E_2 = \emptyset$. Let $E_k \in [U_{k-1}, U_k) \subseteq [U_{n-k}, U_{n-l})$, and $E_1 \in [U_{n-k}, U_{n-l})$, then

$$\begin{aligned} P\left(E_k/E\right) &= P\left(U_{k-1} \leq D \leq U_k / D \leq U_n\right) \\ &= \frac{D\left(A_1, B_1/U_k\right) - D\left(A_1, B_1/U_{k-1}\right)}{D\left(A_1, B_1/U_n\right)} \\ &= \int_0^{U_k} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right]^{-1} \\ &\quad - \int_0^{U_{k-1}} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right].^{-1} \end{aligned} \tag{2.6}$$

Suppose $E_k \in [U_{k-1}, U_k) \subseteq [U_{n-k}, U_{n-l})$, and $E_2 \in [U_{n-k}, U_{n-l})$ i.e a situation when $Z_1 > Z_2$, then

$$P(E_k/E) = \int_0^{U_k} h(t/A_2)G(t-s/B_2)ds. \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)ds\right]^{-1}$$

$$- \int_0^{U_{k-1}} h(t/A_2)G(t-s/B_2)ds. \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)ds\right]^{-1}. \quad (2.7)$$

Let $E_l \in [U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$, and $E_2 \in [U_{n-l}, U_{n-m})$, then

$$P(E_l/E) = P(U_{l-1} \leq D \leq U_l / D \leq U_n)$$

$$= \frac{D(A_2, B_2/U_l) - D(A_2, B_2/U_{l-1})}{D(A_2, B_2/U_n)}$$

$$= \int_0^{U_l} h(t/A_2)G(t-s/B_2)ds. \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)ds\right]^{-1}$$

$$- \int_0^{U_{l-1}} h(t/A_2)G(t-s/B_2)ds. \left[\int_0^{U_n} h(t/A_2)G(t-s/B_2)ds\right].^{-1} \quad (2.8)$$

Suppose $E_l \in [U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$, and $E_1 \in [U_{n-l}, U_{n-m})$ i.e a situation when $Z_1 > Z_2$, then

$$P(E_l/E) = \int_0^{U_l} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right]^{-1}$$

$$- \int_0^{U_{l-1}} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right]^{-1}. \quad (2.9)$$

Now consider $E_1 = E_2 \in [U_{p-1}, U_p) \subseteq [U_{n-k}, U_{n-m})$, i.e. $Z_1 = Z_2$, then the conditional probabilities contain the same parameter sets. In this situation,

$$P(E_p/E) = \int_0^{U_p} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right]^{-1}$$

$$- \int_0^{U_{p-1}} h(t/A_1)G(t-s/B_1)ds. \left[\int_0^{U_n} h(t/A_1)G(t-s/B_1)ds\right]^{-1}. \quad (2.10)$$

Since $Z_3 > Z_0, Z_1, Z_2$, suppose $E_3 \in [U_{m-1}, U_m) \subseteq [U_{n-m}, U_n]$, then

$$P\left(U_{m-1} \leq D \leq U_m/D \leq U_n\right) = \frac{D\left(A_3, B_3/U_m\right) - D\left(A_3, B_3/U_{m-1}\right)}{D\left(A_3, B_3/U_n\right)}.$$

Therefore,

$$\begin{aligned} P\left(E_m/E\right) &= \int_0^{U_m} h(t/A_3)G(t-s/B_3)ds. \left[\int_0^{U_n} h(t/A_3)G(t-s/B_3)ds\right]^{-1} \\ &\quad - \int_0^{U_{m-1}} h(t/A_3)G(t-s/B_3)ds. \left[\int_0^{U_n} h(t/A_3)G(t-s/B_3)ds\right]^{-1} \end{aligned} \tag{2.11}$$

The above conditional probabilities $P\left(E_j/E\right), P\left(E_k/E\right), P\left(E_l/E\right), P\left(E_p/E\right)$ and $P\left(E_m/\mathbf{E}\right)$ are the probabilities associated with the intervals $[U_{j'-1}, U_{j'})$, $[U_{k'-1}, U_{k'})$, $[U_{l'-1}, U_{l'}), [U_{p'-1}, U_{p'})$ and $[U_{m'-1}, U_{m'})$ for the ranges of j, k, l, p and m defined above. Since, $X_0, X_1, X_2, ..., X_{n-k}, ..., X_{n-l}, ..., X_{n-m}, ..., X_n$are mutually exclusive, we assume they follow a parametric distribution with the above probabilitiesare mutually exclusive, so we assume they follow the multinomial property of the distribution of the values in the time intervals and the above conditional probabilities. Then the likelihood functions corresponding to the event set $\mathbf{E}$ are $L_0\left(\mathbf{A}, \mathbf{B}/P_j\right) = \prod_{j'=1}^{n-k} P_j\left(\mathbf{A}, \mathbf{B}/T_{j'}\right)$, $L_{1(2)}\left(\mathbf{A}, \mathbf{B}/P_k\right) = \prod_{k'=n-k}^{n-l} P_{k'}\left(\mathbf{A}, \mathbf{B}/T_{k'}\right)$, $L_{2(1)}\left(\mathbf{A}, \mathbf{B}/P_{l'}\right) = \prod_{l'=n-l}^{n-m} P_{l'}\left(\mathbf{A}, \mathbf{B}/T_{l'}\right)$, $L_{1=2}\left(\mathbf{A}, \mathbf{B}/P_p\right) = \prod_{p'=n-k}^{n-m} P_{p'}\left(\mathbf{A}, \mathbf{B}/T_{p'}\right)$ and $L_3\left(\mathbf{A}, \mathbf{B}/P_m\right) = \prod_{m'=n-m}^{n} P_{m'}\left(\mathbf{A}, \mathbf{B}/T_{m'}\right)$. Here $P_\bullet = P(E_\bullet/\mathbf{E})$. We estimate $\mathbf{A}$ by fitting an infection curve from the incidence data and we then estimate $\mathbf{B}$ by maximizing the likelihood functions expressed above. The best estimate of $\mathbf{A}$ could be information for initial values of X and Y in the model (1.3). Using the corresponding estimate of $\mathbf{B}$, we obtain $\int_{\mathbb{R}} z_i dF(z_i)$. In such situations, the above likelihood functions would be $L_0 = \prod_{j'=0}^{n-k} P_j^{T_{j'}}$, $L_{1(2)} = \prod_{k'=n-k}^{n-l} P_k^{T_{k'}}$,$L_{2(1)} = \prod_{l'=n-l}^{n-m} P_l^{T_{l'}}$, $L_{1=2} = \prod_{p'=n-k}^{n-m} P_p^{T_{p'}}$ and $L_3 = \prod_{m'=n-m}^{n} P_m^{T_{m'}}$.

3. Generalization for multiple drug impact

In this section, expressions for the conditional probabilities are presented when multiple drugs are administrated in the population. Let $N = \{N_0, N_1, N_2, ..., N_N\}$ be the number of available drugs and $Z = \{Z_0, Z_1, Z_2, ..., Z_N\}$ be their corresponding incubation periods. Further let $Z_0 < Z_1 < Z_2 <, ..., < Z_N$ and $\mathbf{A}$ and $\mathbf{B}$ be their parametric sets. Then

$$
\begin{aligned}
D\left(\mathbf{A},\mathbf{B}/U_{N_N}\right) &= \int_0^{U_{N_0}} h(t/A_{N_0})G(t-s/B_{N_0})ds \\
&\quad + \int_{U_{N_0}}^{U_{N_1}} h(t/A_{N_1})G(t-s/B_{N_1})ds \\
&\quad \cdots + \int_{U_{N_{N-1}}}^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds. \qquad (3.1)
\end{aligned}
$$

Now, $P\left(E_{N_i}/E\right) = P\left(U_{N_{i-1}} \leq D \leq U_{N_i}/D \leq U_{N_N}\right)$ and L_{N_i} (for some i) can be computed as follows:

$$
\begin{aligned}
P\left(E_{N_i}/E\right) &= \int_0^{U_{N_i}} h(t/A_{N_i})G(t-s/B_{N_i})ds \times \\
&\quad \left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds\right]^{-1} \\
&\quad - \int_0^{U_{N_{i-1}}} h(t/A_{N_{i-1}})G(t-s/B_{N_{i-1}})ds \times \\
&\quad \left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds\right].^{-1} \qquad (3.2)
\end{aligned}
$$

$L_{N_i} = \prod_{j=N_{i-1}}^{N_i} P_j^{T_j}$ is maximized for the set $[A_i, B_i]$ by the procedure explained in the previous section. We will obtain N sets of $[\mathbf{A},\mathbf{B}]$ values, and the corresponding likelihood values are $L_{N_1}, L_{N_2}, L_{N_3}, ..., L_{N_N}$. In the above, we have assumed monotinicity of (Z_i) to arrive at (3.2). If the (Z_i) values are not monotonic then the various conditional probabilities can be constructed as explained in the previous section. There we explained the general expression when there were a finite number of drugs available on the market. A detailed construction of various conditional probabilities is not necessary for the purpose of the present section (for details see Appendix I). When the $Z_i s$ are not monotonic, and if they follow some order, say for example, $Z_0 > Z_1 < Z_2 > ... < Z_N$, then the conditional probabilities can be constructed in the same way as equations (2.7-2.9) were. Suppose (Z_p) are equal for each p, then there will be two scenarios arising: one for before drug intervention and one after drug intervention. For this situation, the likelihood equation is $L_{N_p} = \prod_{p=N_{p-1}}^{N_p} P_p^{T_p}$ where $P\left(E_{N_p}/E\right)$, is given as follows:

$$
\begin{aligned}
P\left(E_{N_p}/E\right) &= \int_0^{U_{N_p}} h(t/A_{N_p})G(t-s/B_{N_p})ds \times \\
&\quad \left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds\right]^{-1} \\
&\quad - \int_0^{U_{N_{p-1}}} h(t/A_{N_{p-1}})G(t-s/B_{N_{p-1}})ds \times \\
&\quad \left[\int_0^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds\right]. \qquad (3.3)
\end{aligned}
$$

4. Theoretical examples

In this section, we show some examples of the likelihood function constructed in the previous section, to estimate **A**, and **B**. Let $h(s)$ follow a quadratic exponential and **B** follow a) a gamma function, and b) a logistic function. Infections in most of the countries started declining after the availability of antiretroviral therapies (see Conti, S et al (2000), Hung, C-C et al (2003)), and incidence in the recent period was found to be stable in some countries like India (Rao et al (2006)). This motivated us to choose a quadratic exponential to represent $h(s)$, namely $h(s) = exp(\alpha_1 s^2 + \alpha_2 s + \alpha_3)$ for all $-\infty < \alpha_1, \alpha_2, \alpha_3 < \infty$. A quadratic exponential function has been shown to be a good model for representing the above declines in the incidence rates (see Rao and Kakehashi, 2005). The incubation period for AIDS is large as well as variable, therefore, functions like the gamma, Weibull and logistic can mimic several shapes to fit the incubation period data depending on their parameter values. Such well-known functions were used by many researchers for modeling the incubation period of AIDS. We now demonstrate the application of such functions for the theory explained in section 2.

4.1. **Example 1: Gamma function.** If $\omega > 0$ is the parameter and $\Gamma(\omega)$ is the complete distribution function, then the incomplete gamma distribution, $G(\omega; t_j) = \frac{1}{\Gamma(\omega)} \int_0^{t_j} e^{-x} x^{\omega-1} dx$, for $a \geq 0, t_j \geq 0$ and $a + t_j \neq 0$. From the conditional probability equations from (2.5) to (2.11), and the likelihood equations explaind in the later part of section 3, the following are the likelihood equations without a drug and for with three types of drugs:

$$
L_0\left(\alpha_1, \alpha_2, \alpha_3; \omega/P_j\right) = \prod_j a_1(j)a_2(j) - \prod_j a_1(j-1)a_2(j) \qquad (4.1)
$$

where

$$\begin{aligned} a_1(j) &= \left[\int_0^{u_j} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_j} e^{-(u_j-s)}(u_j-s)^{\omega-1}du_j\right\}ds\right]^{T_j} \\ a_1(j-1) &= \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\right. \\ &\qquad \left.\times\left\{\frac{1}{\Gamma\omega}\int_0^{t_{j-1}} e^{-(u_{j-1}-s)}(u_{j-1}-s)^{\omega-1}du_{j-1}\right\}ds\right]^{T_j} \\ a_2(j) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_n} e^{-(u_n-s)}(u_n-s)^{\omega-1}du_n\right\}ds\right]^{-T_j} \end{aligned}$$

$$L_{1(2)}\left(\alpha_1,\alpha_2,\alpha_3;\omega/P_k\right) = \prod_k a_1(k)a_2(k) - \prod_k a_1(k-1)a_2(k) \tag{4.2}$$

where

$$\begin{aligned} a_1(k) &= \left[\int_0^{u_k} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_k} e^{-(u_k-s)}(u_k-s)^{\omega-1}du_k\right\}ds\right]^{T_k} \\ a_1(k-1) &= \left[\int_0^{u_{k-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\right. \\ &\qquad \left.\times\left\{\frac{1}{\Gamma\omega}\int_0^{t_{k-1}} e^{-(u_{k-1}-s)}(u_{k-1}-s)^{\omega-1}du_{k-1}\right\}ds\right]^{T_k} \\ a_2(k) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_n} e^{-(u_n-s)}(u_n-s)^{\omega-1}du_n\right\}ds\right]^{-T_k} \end{aligned}$$

$$L_{2(1)}\left(\alpha_1,\alpha_2,\alpha_3;\omega/P_l\right) = \prod_l a_1(l)a_2(l) - \prod_l a_1(l-1)a_2(l) \tag{4.3}$$

where

$$
\begin{aligned}
a_1(l) &= \left[\int_0^{u_l} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_l} e^{-(u_l-s)}(u_l-s)^{\omega-1}du_l\right\}ds\right]^{T_l} \\
a_1(l-1) &= \left[\int_0^{u_{l-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\right. \\
&\qquad \left.\times\left\{\frac{1}{\Gamma\omega}\int_0^{t_{l-1}} e^{-(u_{l-1}-s)}(u_{l-1}-s)^{\omega-1}du_{l-1}\right\}ds\right]^{T_l} \\
a_2(l) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_n} e^{-(u_n-s)}(u_n-s)^{\omega-1}du_n\right\}ds\right]^{-T_l}
\end{aligned}
$$

$$
L_{1=2}\left(\alpha_1,\alpha_2,\alpha_3;\omega/P_p\right) = \prod_p a_1(p)a_2(p) - \prod_p a_1(p-1)a_2(p) \tag{4.4}
$$

where

$$
\begin{aligned}
a_1(p) &= \left[\int_0^{u_p} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_p} e^{-(u_p-s)}(u_p-s)^{\omega-1}du_p\right\}ds\right]^{T_p} \\
a_1(p-1) &= \left[\int_0^{u_{p-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\right. \\
&\qquad \left.\times\left\{\frac{1}{\Gamma\omega}\int_0^{t_{p-1}} e^{-(u_{p-1}-s)}(u_{p-1}-s)^{\omega-1}du_{p-1}\right\}ds\right]^{T_p} \\
a_2(p) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_n} e^{-(u_n-s)}(u_n-s)^{\omega-1}du_n\right\}ds\right]^{-T_p}
\end{aligned}
$$

$$
L_3\left(\alpha_1,\alpha_2,\alpha_3;\omega/P_m\right) = \prod_m a_1(m)a_2(m) - \prod_m a_1(m-1)a_2(m) \tag{4.5}
$$

where

$$
\begin{aligned}
a_1(m) &= \left[\int_0^{u_m} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_m} e^{-(u_m-s)}(u_m-s)^{\omega-1}du_m\right\}ds\right]^{T_m} \\
a_1(m-1) &= \left[\int_0^{u_{m-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\right. \\
&\qquad \left.\times\left\{\frac{1}{\Gamma\omega}\int_0^{t_{m-1}} e^{-(u_{m-1}-s)}(u_{m-1}-s)^{\omega-1}du_{m-1}\right\}ds\right]^{T_m} \\
a_2(m) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\frac{1}{\Gamma\omega}\int_0^{t_n} e^{-(u_n-s)}(u_n-s)^{\omega-1}du_n\right\}ds\right]^{-T_m}
\end{aligned}
$$

4.2. **Example 2: Logistic function.** Suppose θ_1, θ_2 are parameters and $F(\theta_1, \theta_2; t_j) = \left\{1 + e^{-(\frac{t_j-\theta_1}{\theta_2})}\right\}^{-1}$, for $\theta_1, \theta_2 > 0$, is the distribution function. The likelihood equations to obtain the parameters of logistic distribution without drugs and for three types of drugs are as follows:

$$
L_0\left(\alpha_1, \alpha_2, \alpha_3; \theta_1, \theta_2/P_j\right) = \prod_j a_1'(j)a_2'(j) - \prod_j a_1'(j-1)a_2'(j) \tag{4.6}
$$

where

$$
\begin{aligned}
a_1'(j) &= \left[\int_0^{u_j} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_j-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_j} \\
a_1'(j-1) &= \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_{j-1}-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_j} \\
a_2'(j) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_n-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{-T_j}
\end{aligned}
$$

$$
L_{1(2)}\left(\alpha_1, \alpha_2, \alpha_3; \theta_1, \theta_2/P_k\right) = \prod_k a_1'(k)a_2'(k) - \prod_k a_1'(k-1)a_2'(k) \tag{4.7}
$$

where

$$
\begin{aligned}
a_1'(k) &= \left[\int_0^{u_k} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_k-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_k} \\
a_1'(k-1) &= \left[\int_0^{u_{k-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_{k-1}-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_k} \\
a_2'(k) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_n-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{-T_k}
\end{aligned}
$$

$$
L_{2(1)}\left(\alpha_1,\alpha_2,\alpha_3;\theta_1,\theta_2/P_l\right) = \prod_l a_1'(l)a_2'(l) - \prod_l a_1'(l-1)a_2'(l) \tag{4.8}
$$

where

$$
\begin{aligned}
a_1'(l) &= \left[\int_0^{u_l} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_l-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_l} \\
a_1'(l-1) &= \left[\int_0^{u_{l-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_{l-1}-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_l} \\
a_2'(l) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_n-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{-T_l}
\end{aligned}
$$

$$
L_{1=2}\left(\alpha_1,\alpha_2,\alpha_3;\theta_1,\theta_2/P_p\right) = \prod_p a_1'(p)a_2'(p) - \prod_p a_1'(p-1)a_2'(p) \tag{4.9}
$$

where

$$
\begin{aligned}
a_1'(p) &= \left[\int_0^{u_p} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_p-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_p} \\
a_1'(p-1) &= \left[\int_0^{u_{p-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_{p-1}-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_p} \\
a_2'(p) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_n-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{-T_p}
\end{aligned}
$$

$$(4.10)L_3\left(\alpha_1,\alpha_2,\alpha_3;\theta_1,\theta_2/P_m\right) = \prod_m a_1'(m)a_2'(m) - \prod_m a_1'(m-1)a_2(m)$$

where

$$\begin{aligned} a_1'(m) &= \left[\int_0^{u_m} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_m-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_m} \\ a_1'(m-1) &= \left[\int_0^{u_{m-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_{m-1}-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{T_m} \\ a_2'(m) &= \left[\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{\left\{1+e^{-(\frac{u_n-\theta_1}{\theta_2})}\right\}^{-1}\right\}ds\right]^{-T_m} \end{aligned}$$

4.3. **Example 3: Log-normal function.** Suppose μ and σ are parameters and $LNF(\mu,\sigma;t_j) = \frac{1}{2}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}$, for $\mu,\sigma>0$, is the distribution function. (Here $erf\{.\}$ is the error function of the Gaussian function). The likelihood equations to obtain the parameters of the logistic distribution without drugs and for three types of drugs are as follows:

$$(4.11)\quad L_0\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_j\right) = \prod_j a_1''(j)a_2''(j) - \prod_j a_1''(j-1)a_2''(j)$$

where

$$\begin{aligned} a_1''(j) &= \left[\frac{1}{2}\int_0^{u_j} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_j} \\ a_1''(j-1) &= \left[\frac{1}{2}\int_0^{u_{j-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_j} \\ a_2''(j) &= \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_j} \end{aligned}$$

$$(4.12)\ L_{1(2)}\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_k\right) = \prod_k a_1''(k)a_2''(k) - \prod_k a_1''(k-1)a_2''(k)$$

where

$$
\begin{aligned}
a_1''(k) &= \left[\frac{1}{2}\int_0^{u_k} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_k} \\
a_1''(k-1) &= \left[\frac{1}{2}\int_0^{u_{k-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_k} \\
a_2''(k) &= \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_k}
\end{aligned}
$$

$$
L_{2(1)}\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_l\right) = \prod_l a_1''(l)a_2''(l) - \prod_l a_1''(l-1)a_2''(l) \tag{4.13}
$$

where

$$
\begin{aligned}
a_1''(l) &= \left[\frac{1}{2}\int_0^{u_l} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_l} \\
a_1''(l-1) &= \left[\frac{1}{2}\int_0^{u_{l-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_l} \\
a_2''(l) &= \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_l}
\end{aligned}
$$

$$
L_{1=2}\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_p\right) = \prod_p a_1''(p)a_2''(p) - \prod_p a_1''(p-1)a_2''(p) \tag{4.14}
$$

where

$$
\begin{aligned}
a_1''(p) &= \left[\frac{1}{2}\int_0^{u_p} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_p} \\
a_1''(p-1) &= \left[\frac{1}{2}\int_0^{u_{p-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_p} \\
a_2''(p) &= \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_p}
\end{aligned}
$$

$$
L_3\left(\alpha_1,\alpha_2,\alpha_3;\mu,\sigma/P_m\right) = \prod_m a_1'(m)a_2'(m) - \prod_m a_1'(m-1)a_2(m) \tag{4.15}
$$

where

$$
\begin{aligned}
a_1''(m) &= \left[\frac{1}{2}\int_0^{u_m} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_m} \\
a_1''(m-1) &= \left[\frac{1}{2}\int_0^{u_{m-1}} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{T_m} \\
a_2''(m) &= \left[\frac{1}{2}\int_0^{u_n} e^{\alpha_1 s^2+\alpha_2 s+\alpha_3}\left\{1+erf\left(\frac{\ln x-\mu}{\sigma\sqrt{2}}\right)\right\}ds\right]^{-T_m}
\end{aligned}
$$

5. Models for Drug efficacy

In the past 10-12 years there have been models developed to study HIV dynamics in *vivo* and the role of drugs in changing the virus dynamics inside the human body. In this section we outline such models given by others and explain how specific drugs intervene the standard dynamics (For details on the models given in this section see Ho et al (1995), Wei et al (1995), Perelson and Nelson (1999), Ferguson et al (1999) and Nowak and May (2000)).

Let X_1, $Y_1$and Z_1 represents variables corresponding to uninfected T cells, infected T cells and HIV virus in the serum. Then the system explaining the dynamics of these variables is given by

$$
\begin{aligned}
\frac{dX_1}{dt} &= \lambda_1 - \mu_x X - (1-\xi_R)\beta_1 XZ \\
\frac{dY_1}{dt} &= (1-\xi_R)\beta_1 XZ - \mu_1 Y \\
\frac{dZ_1}{dt} &= M\mu_1 Y_1 - c_1 Z_1
\end{aligned} \tag{5.1}
$$

Here the parameter for reverse transcriptase drug (i.e. anti-retroviral therapy) is $\xi_R \in [0,1]$. A value of 0 indicates no effect of the drug in blocking the virus from infecting an uninfected cell, and 1 indicates that the drug is blocking the virus with 100 per cent effectiveness. λ_1 is the rate of generation of new target cells, μ_x is the death rate of these uninfected target cells and β_1 is the rate at which virus particles infect these uninfected target cells. Once the cells are infected it is assumed that they will die at a rate μ_1 due to the immune system or the virus. This is based on the assumption that the probability of cell death at time t is given by an exponential distribution with an average lifetime of $1/\mu_x$ for uninfected cells and $1/\mu_1$ for the infected cells. It is also assumed that an infected cell will produce M new virus particles during their lifetime, so this number multiplied by the average life time gives the average rate of virus production i.e. $M\mu_1$. Lastly, c_1 is the constant clearance rate at which

virus particles are cleared from the system. The steady state solutions for the model (5.1) are $X_1^* = \lambda_1/\mu_x,\ Y_1^* = 0,\ Z_1^* = 0$ and $X_1^* = c_1/M\beta_1(1-\xi_R),\ Y_1^* = (\lambda_1/\mu_1)\,(1-1/R_0)$, $Z_1^* = (\lambda_1 M\beta_1(1-\xi_R) - \mu_x c_1)\,/\beta_1(1-\xi_R)c_1$. The basic reproductive rate for the model (5.1) is $R_0 = \lambda_1 M\beta_1\,(1-\xi_R)\,/\mu_x c_1$ and will be nullified when reverse transcriptase is successful. The solution will be stable when $R_0 > 1$.

When protease inhibitors are introduced we will have four variables in the system. Infected cell will produce infectious virus and non-infectious virus due to drug intervention. Let Z_I and Z_{NI} be the variables corresponding to infected and non-infected virus. If β_2 and β_3 are the infection rates, then $\beta_2 X_1 Z_I$ is the mass action term and $\beta_3 = 0$ due to drugs. Before giving the drug, whatever infectious virus is there will be there for some time and infect other cells. In the blood plasma there will be a concentration of infectious virus particles Z_I and noninfectious virus particles Z_{NI} ($Z = Z_I + Z_{NI}$). Quantitatively, assume that 100 percent effective PI is given, then it will not have any impact on producing infected T cells from the virus, but it will have impact on infected T cells and block production of Z_I, and only Z_{NI} is produced. And whatever infectious virus remaining in the blood plasma will be there for a short time and will be cleared exponentially, i.e. $Z_I(t) = Z_0 e^{-c_1 t}$. Then the basic model for the virus dynamics becomes

$$
\begin{aligned}
\frac{dX_1}{dt} &= \lambda_1 - \mu_x X_1 - \beta_2 X_1 Z_I - o(\beta_3 X_1 Z_{NI}) \\
\frac{dY_1}{dt} &= \beta_2 X_2 Z_I - \mu_1 Y_1 \\
\frac{dZ_I}{dt} &= -c_1 Z_I \qquad (5.2) \\
\frac{dZ_{NI}}{dt} &= M\mu_1 Y_1 - c_1 Z_{NI}
\end{aligned}
$$

The assumption of 100 percent efficacy in protease inhibitors is not realistic, so an effectiveness factor, ξ_P is introduced in the system (Perelson and Nelson, 1999) as follows

$$
\begin{aligned}
\frac{dX_1}{dt} &= \lambda_1 - \mu_x X_1 - \beta_2 X_1 Z_I \\
\frac{dY_1}{dt} &= \beta_2 X_1 Z_I - \mu_1 Y_1 \\
\frac{dZ_I}{dt} &= (1-\xi_P) M \mu_1 Y_1 - c_1 Z_I \\
\frac{dZ_{NI}}{dt} &= \xi_P M \mu_1 Y_1 - c_1 Z_{NI}
\end{aligned} \tag{5.3}
$$

The steady state solutions for the model (5.3) are $X_1^* = \lambda_1/\mu_x$, $Y_1^* = 0$, $Z_1^* = 0$, $X_1^* = c_1/M\beta_2\,(1-\xi_P)$, $Y_1^* = (\lambda_1/\mu_1)\ (1-1/R_0)$, $Z_I^* = (\lambda_1/c_1)\ (1-\xi_P)\,M - (\mu_x/\beta_2)$ and $Z_{NI}^* = \lambda_1 M\xi_P/c_1\,(1-1/R_0)$. Here $R_0 = \lambda_1 M\beta_2\ (1-\xi_P)\,/\mu_x c_1$. The basic reproductive rate is mathematically not different for RT and PI. In other words, the reduction in R_0 will be same as that of efficacy due to RT intervention. Herz et al (1996) discuss the alternatives of prescribing both anti-retroviral therapy and protease inhibitors simultaneously. We assumed this double therapy is more effective than single theray in our analysis presented in sections 2 and 3.

6. Age-structured populations

In this section we extend the models 1.3 and 1.4 to accommodate age structure into the population mixing and epidemiology parameters. The incubation period for children is shorter than that of adults. Within the adult population there could be variability due to age at the time of infection. There are studies that analyse the HIV data on age collected at the time of infection to study parameters like incubation period (Becker et al, 2003), and some studies incorporate age structure in the models to explain the impact of an age-dependent incubation period (Griffits, 2000). In the absence of availability of cohort data, the methods explained in section 2 could be of great use to estimate the incubation period. The analysis and method explained there could be done for individuals of each age (single ages). However, we describe the age-structure model and the method to obtain the incubation period in this section by considering j age groups. In a hospital set-up it is relatively easy to follow cohorts of age groups compared to following cohorts of individuals for each age group.

Suppose the population in the j^{th} age group is divided into X_j susceptible, $Y_{0,j}$, $Y_{1,j}$, $Y_{2,j}$, $Y_{3,j}$ are infected and $D_{z_0,j}$, $D_{z_1,j}$, $D_{z_2,j}$, $D_{z_3,j}$ individuals with the disease without drugs, and for *drug1, drug2, drug3* respectively. The differential equations explaining these variables are

$$
\begin{aligned}
\frac{dX_j}{dt} &= \Lambda_j - \left(\lambda_{jk}^0 + \lambda_{jk}^1 + \lambda_{jk}^2 + \lambda_{jk}^3 + \mu_j\right) X_j, \\
\frac{dY_{0,j}}{dt} &= \lambda_{jk}^0 X_j - \left\{ \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} + \mu_j \right\} Y_{0,j}, \\
\frac{dY_{1,j}}{dt} &= \lambda_{jk}^1 X_j - \left\{ \left(\int_{\mathbb{R}} z_{1,j} dG(z_{1,j}) \right)^{-1} + \mu_j \right\} Y_{1,j}, \\
\frac{dY_{2,j}}{dt} &= \lambda_{jk}^2 X_j - \left\{ \left(\int_{\mathbb{R}} z_{2,j} dG(z_{2,j}) \right)^{-1} + \mu_j \right\} Y_{2,j}, \\
\frac{dY_{3,j}}{dt} &= \lambda_{jk}^3 X_j - \left\{ \left(\int_{\mathbb{R}} z_{3,j} dG(z_{3,j}) \right)^{-1} + \mu_j \right\} Y_{3,j}, \\
\frac{dD_{z_0,j}}{dt} &= \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} Y_{0,j} - \gamma_{0,j} D_{z_0,j} \\
\frac{dD_{z_1,j}}{dt} &= \left(\int_{\mathbb{R}} z_{1,j} dG(z_{1,j}) \right)^{-1} Y_{1,j} - \gamma_{1,j} D_{z_1,j} \\
\frac{dD_{z_2,j}}{dt} &= \left(\int_{\mathbb{R}} z_{2,j} dF(z_{2,j}) \right)^{-1} Y_{2,j} - \gamma_{2,j} D_{z_2,j} \\
\frac{dD_{z_3,j}}{dt} &= \left(\int_{\mathbb{R}} z_{3,j} dG(z_{3,j}) \right)^{-1} Y_{3,j} - \gamma_{3,j} D_{z_3,j}.
\end{aligned} \tag{6.1}
$$

Here, Λ_j is the input of susceptibles for the individuals in the age group j, μ_j is the mortality rate, λ_{jk}^0,λ_{jk}^1 ,λ_{jk}^2 and λ_{jk}^3 are the forces of infection at which a susceptible in the age group j is infected by an infected individual in the age group k and$\gamma_{0,j}$, $\gamma_{1,j}$, $\gamma_{2,j}$ and $\gamma_{3,j}$ are disease related mortality rates for the infected individuals in the age group j without drugs, and with *drug1, drug2, and drug3* for the individuals. $\left(\int_{\mathbb{R}} z_{i,j} dG(z_{i,j})\right)^{-1}$ is the rate of disease progression for the infected individual for the age group j for the drug type i.

If there are n drug types available then the general model describing the dynamics of various variables described above is as follows:

$$
\begin{aligned}
\frac{dX_j}{dt} &= \Lambda_j - \left(\lambda_{jk}^0 + \lambda_{jk}^1 + \lambda_{jk}^2 + \lambda_{jk}^3 + \mu_j\right) X_j, \\
\frac{dY_{0,j}}{dt} &= \lambda_{jk}^0 X_j - \left\{ \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} + \mu_j \right\} Y_{0,j}, \\
&\vdots \quad\quad \vdots \\
&\vdots \quad\quad \vdots \\
\frac{dY_{n,j}}{dt} &= \lambda_{jk}^n X_j - \left\{ \left(\int_{\mathbb{R}} z_{n,j} dG(z_{n,j}) \right)^{-1} + \mu_j \right\} Y_{n,j}, \\
\frac{dD_{z_0,j}}{dt} &= \left(\int_{\mathbb{R}} z_{0,j} dG(z_{0,j}) \right)^{-1} Y_{0,j} - \gamma_{0,j} D_{z_0,j}, \\
&\vdots \quad\quad \vdots \\
&\vdots \quad\quad \vdots \\
\frac{dD_{z_n,j}}{dt} &= \left(\int_{\mathbb{R}} z_{n,j} dG(z_{n,j}) \right)^{-1} Y_{n,j} - \gamma_{n,j} D_{z_n,j}.
\end{aligned} \tag{6.2}
$$

where $\alpha_{i,j}$ is the mortality rate of infected individuals of drug type i in the age group j.

6.1. **Varying incubation periods for age-structured populations.** We are interested in the average incubation period for a group of individuals in the age group j. If $H(j)$ is the time of infection and $Z(j)$ is the incubation period for the j^{th} age group, then the time of onset of the disease for this age group is $D(j) = H(j) + Z(j)$. This is the time of onset of the disease for an individual who acquired the infection while in the j^{th} age group. Development of the disease will be some time units (for example: months, years) after infection at age j. An individual who acquired the infection at age j is assumed to develop the full disease before completion of the same age j or $> j$. Given $H(j)$, for some j, then $D(j)$ is allowed to occur at age $j'(j' = j, j+1, \cdots, j+\omega$, where $j+\omega$ is the last age group for the possibility of infection). Clearly, $H(j) \leq D(j)$. $H(j) = D(j)$ is possible if an individual acquired infection and attains disease before completion of age j. One can do analysis using a bi-annual (or half-yearly) ageing process.

Consider an infection and disease development matrix (see figure 2) where each cell (j, j') denotes the (infection age groups, disease onset age groups) for $j = 0, 1, 2, ..., j+\omega$; $j' = 0, 1, 2, ..., j+\omega$. Only those cells for which $j \leq j'$ are provided, and other cells are left blank for which the incubation period is not defined. In the matrix, all the eligible cells are denoted, so obviously there are

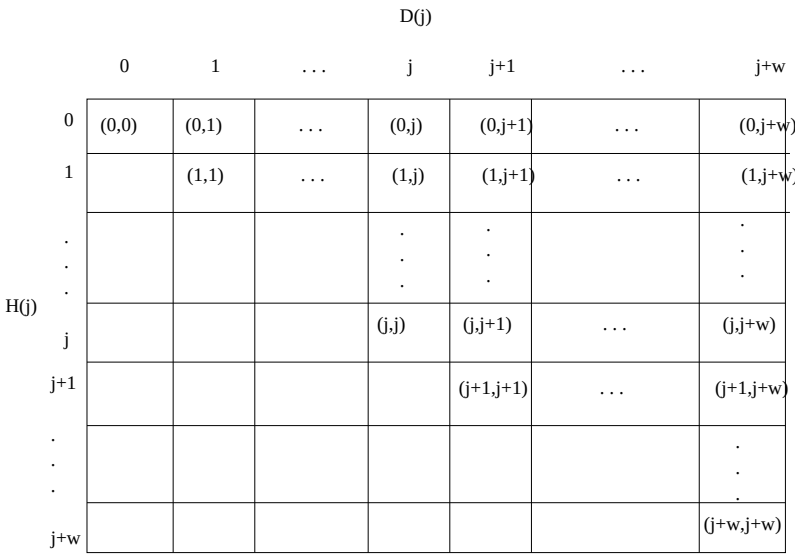

FIGURE 6.1. Age-structured infection and disease development matrix. Here row values indicate infection age group ($H(j)$) and column values for age group in which infected individual developed disease ($D(j)$). An individual who acquired the infection in j, and developed disease in $j+\omega$, is indicated by the cell $(j, j+\omega)$.

more cells present where the condition $j \leq j'$ is satisfied, and also j is very low. (In fact, the average incubation period is not beyond a certain duration. It is not intended in the matrix to suggest that the lower the value of j then the larger the value of incubation period). If the age of infection is higher, for some j, and towards the last few possible age groups, then it is possible that $j'-j$ is shorter because individuals die naturally in old age. At the same time, the chance of infection in the very higher age groups (say $60+$) is negligible for HIV (unless there are some rare causes). In the absense of age specific cohorts of infected individuals and follow-up data, it is not feasible to calculate disease progression rates and survival probabilities using direct cohort methods. In this section, we extend the method given in section 2 to estimate the average disease progression rates (or average incubation periods) for infections in age group j. This method is dependent on infection densities and data on disease occurances for the age group j.

Let $p(t, j)$ and $q(t, j)$ be the probability density functions of infection density and incubation period for the age group j. If $Q(t, j)$ is the distribution function of the incubation period, then $Q(t, j) = \int_{-\infty}^{t} q(t, j)dt$. Now, the convolution of $p(t, j)$ and $Q(t, j)$ is given by

$$C(s,t) \;=\; \int_{-\infty}^{\infty} p(t,j)Q(t-s,j)ds.$$

We call C the convolution of p and Q (i.e. $p*Q$, where $*$ is the convolution operator). Therefore,

$$p*Q \;=\; \int_{-\infty}^{\infty} p(t,j)Q(t-s,j)ds.$$

Suppose an individual is diagnosed with a disease at age j in the year U_k. Then there is a possibility that this individual acquired the infection in any of the years prior to U_k (provided this individual is born in the year $\geq U_0$). Similarly, all those individuals who are diagnosed with the disease at age $j+w$ in the year U_n have actually acquired infection in any of the years from U_0 to U_n. In the same way, an individual infected at age j will be diagnosed with the disease in an age group $\geq j$. We consider model (6.1), where four types of drugs were considered in section 2.

Let $A_0(j)$,$A_1(j)$, $A_2(j)$,$A_3(j)$ be the parameter sets in age group j for the four kind of drugs. Let $B_0(j)$,$B_1(j)$, $B_2(j)$,$B_3(j)$ be the parameter sets C and $E_0(j)$,$E_1(j)$, $E_2(j)$,$E_3(j)$ be the corresponding events of diagnosis of disease in the age group j for the four types of drugs. The cumulative number of diagnosed disease cases up to U_n for individuals who are diagnosed in the age group j is

$$J(U_0 < s < U_n, j) \;=\; \sum_{j*=0}^{j} I(j*,j),$$

where $I(0,j), I(1,j), ..., I(j,j)$ are the numbers of disease cases diagnosed in age group j, and acquired the infection in the age group $0, 1, ..., j$.

$$\begin{aligned} I(0,j) \;&=\; \int_0^{U_{n-k}} p(t,0)Q(t-s,j)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,0)Q(t-s,j)ds \\ &\quad + \int_{U_{n-l}}^{U_{n-m}} p(t,0)Q(t-s,j)ds + \int_{U_{n-m}}^{U_n} p(t,0)Q(t-s,j)ds \\ = \;& \int_0^{U_{n-k}} p(t,0/A_0)Q(t-s,j/B_0)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,0/A_1)Q(t-s,j/B_1)ds \\ &+ \int_{U_{n-l}}^{U_{n-m}} p(t,0/A_2)Q(t-s,j/B_2)ds + \int_{U_{n-m}}^{U_n} p(t,0/A_3)Q(t-s,j/B_3)ds \end{aligned}$$

$$
\begin{aligned}
I(1,j) &= \int_0^{U_{n-k}} p(t,1)Q(t-s,j)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,1)Q(t-s,j)ds \\
&\quad + \int_{U_{n-l}}^{U_{n-m}} p(t,1)Q(t-s,j)ds + \int_{U_{n-m}}^{U_n} p(t,1)Q(t-s,j)ds
\end{aligned}
$$

$$
\begin{aligned}
&= \int_0^{U_{n-k}} p(t,1/A_0)Q(t-s,j/B_0)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,1/A_1)Q(t-s,j/B_1)ds \\
&\quad + \int_{U_{n-l}}^{U_{n-m}} p(t,1/A_2)Q(t-s,j/B_2)ds + \int_{U_{n-m}}^{U_n} p(t,1/A_3)Q(t-s,j/B_3)ds
\end{aligned}
$$

$$\vdots$$

$$
\begin{aligned}
I(j,j) &= \int_0^{U_{n-k}} p(t,j)Q(t-s,j)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,j)Q(t-s,j)ds \\
&\quad + \int_{U_{n-l}}^{U_{n-m}} p(t,j)Q(t-s,j)ds + \int_{U_{n-m}}^{U_n} p(t,j)Q(t-s,j)ds
\end{aligned}
$$

$$
\begin{aligned}
&= \int_0^{U_{n-k}} p(t,j/A_0)Q(t-s,j/B_0)ds + \int_{U_{n-k}}^{U_{n-l}} p(t,j/A_1)Q(t-s,j/B_1)ds \\
&\quad + \int_{U_{n-l}}^{U_{n-m}} p(t,j/A_2)Q(t-s,j/B_2)ds + \int_{U_{n-m}}^{U_n} p(t,j/A_3)Q(t-s,j/B_3)ds
\end{aligned}
$$

Similarly for unstructured populations, we assume that U_{n-k} is the time of the introduction of drugs after the first year of detection of the disease in U_0. If $E_1(j) \in [U_{n-k}, U_{n-l})$ and $E_2(j) \in [U_{n-l}, U_{n-m})$, then $Z_1(j) < Z_2(j)$, otherwise if $E_2(j) \in [U_{n-k}, U_{n-l})$ and $E_1(j) \in [U_{n-l}, U_{n-m})$ then $Z_2(j) < Z_1(j)$. If $E_1(j), E_2(j) \in [U_{n-k}, U_{n-m})$, then $Z_1(j) = Z_2(j)$. Given an individual who was diagnosed with the disease in the age group j before U_n is already developed in one of the four intervals $[U_0, U_{n-k})$, $[U_{n-k}, U_{n-l})$, $[U_{n-l}, U_{n-m})$ and $[U_{n-m}, U_n)$. If $E_0(j) \in [U_{i'-1}, U_{i'}) \subseteq [U_0, U_{n-k})$, (for drug type i'), then the conditional probability of occurence of $E_0(j)$ given $E(j)$ is

$$\begin{aligned} Pr\left[E_0(j)/E(j)\right] &= Pr\left[U_{i'-1} \leq J \leq U_{i'}, j/J \leq U_n\right] \\ &= \frac{J\left[A_0(j), B_0(j)/U_{i'}, j\right] - J\left[A_0(j), B_0(j)/u_{i'-1}, j\right]}{J\left[A_0(j), B_0(j)/U_n, j\right]}, \end{aligned}$$

where J values for $E_0(j)$ are given by:

$$\begin{aligned} J\left[A_0(j), B_0(j)/U_{i'}, j\right] &= \int_0^{U_{i'}} p(t, 0/A_0)Q(t-s, j/B_0)ds \\ + \int_0^{U_{i'}} p(t, 1/A_0)Q(t-s, j/B_0)ds \quad \cdots \quad &+ \int_0^{U_{i'}} p(t, j/A_0)Q(t-s, j/B_0)ds \end{aligned}$$

$$\begin{aligned} J\left[A_0(j), B_0(j)/U_{i'-1}, j\right] &= \int_0^{U_{i'-1}} p(t, 0/A_0)Q(t-s, j/B_0)ds \\ + \int_0^{U_{i'-1}} p(t, 1/A_0)Q(t-s, j/B_0)ds \quad \cdots \quad &+ \int_0^{U_{i'-1}} p(t, j/A_0)Q(t-s, j/B_0)ds \end{aligned}$$

$$\begin{aligned} J\left[A_1(j), B_1(j)/U_n, j\right] &= \int_0^{U_n} p(t, 0/A_0)Q(t-s, j/B_0)ds \\ + \int_0^{U_n} p(t, 1/A_0)Q(t-s, j/B_0)ds \quad \cdots \quad &+ \int_0^{U_n} p(t, j/A_0)Q(t-s, j/B_0)ds \end{aligned}$$

The above probability expressions are for the case without drug interventions. When *drugs* were initiated at U_{n-k}, then these probabilities changed according to the occurence of $E_1(j), E_2(j), E_3(j)$. Suppose $E_1(j) \cap E_2(j) = \emptyset$. If $[U_{k'-1}, U_{k'}) \subseteq [U_{n-k}, U_{n-l})$, and $E_1 \in [U_{n-k}, U_{n-l})$, then

$$\begin{aligned} Pr\left[E_1(j)/E(j)\right] &= Pr\left[U_{k'-1} \leq J \leq U_{k'}, j/J \leq U_n\right] \\ &= \frac{J\left[A_1(j), B_1(j)/U_{k'}, j\right] - J\left[A_1(j), B_1(j)/u_{k'-1}, j\right]}{J\left[A_1(j), B_1(j)/U_n, j\right]}, \end{aligned}$$

where J values for $E_1(j)$ are given by

$$J\left[A_1(j), B_1(j)/U_{k'}, j\right] = \int_0^{U_{k'}} p(t, 0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_{k'}} p(t, 1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_{k'}} p(t, j/A_1)Q(t-s, j/B_1)ds$$

$$J\left[A_1(j), B_1(j)/U_{k'-1}, j\right] = \int_0^{U_{k'-1}} p(t, 0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_{k'-1}} p(t, 1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_{k'-1}} p(t, j/A_1)Q(t-s, j/B_1)ds$$

$$J\left[A_1(j), B_1(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_n} p(t, 1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_n} p(t, j/A_1)Q(t-s, j/B_1)ds$$

In the above, instead of $E_1(j)$, if $E_2 \in [U_{n-k}, U_{n-l})$, then the probabilities would be

$$Pr\left[E_2(j)/E(j)\right] = Pr\left[U_{k'-1} \leq J \leq U_{k'}, j/J \leq U_n\right]$$

$$= \frac{J\left[A_2(j), B_2(j)/U_{k'}, j\right] - J\left[A_2(j), B_2(j)/u_{k'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]},$$

where J values for $E_1(j)$ are given by

$$J\left[A_2(j), B_2(j)/U_{k'}, j\right] = \int_0^{U_{k'}} p(t, 0/A_2)Q(t-s, j/B_2)ds$$

$$+\int_0^{U_{k'}} p(t, 1/A_2)Q(t-s, j/B_2)ds \quad \cdots \quad +\int_0^{U_{k'}} p(t, j/A_2)Q(t-s, j/B_2)ds$$

$$J\left[A_2(j), B_2(j)/U_{k'-1}, j\right] = \int_0^{U_{k'-1}} p(t, 0/A_2)Q(t-s, j/B_2)ds$$

$$+\int_0^{U_{k'-1}} p(t, 1/A_2)Q(t-s, j/B_2)ds \quad \cdots \quad +\int_0^{U_{k'-1}} p(t, j/A_2)Q(t-s, j/B_2)ds$$

$$J\left[A_2(j), B_2(j)/U_n, j\right] = \int_0^{U_n} p(t,0/A_2)Q(t-s, j/B_2)ds$$

$$+\int_0^{U_n} p(t,1/A_2)Q(t-s, j/B_2)ds \qquad +\int_0^{U_n} p(t,j/A_2)Q(t-s, j/B_2)ds$$

If $[U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$, and $E_1 \in [U_{n-l}, U_{n-m})$, then

$$Pr\left[E_1(j)/E(j)\right] = Pr\left[U_{l'-1} \leq J \leq U_{l'}, j/J \leq U_n\right]$$

$$= \frac{J\left[A_1(j), B_1(j)/U_{l'}, j\right] - J\left[A_1(j), B_1(j)/u_{l'-1}, j\right]}{J\left[A_1(j), B_1(j)/U_n, j\right]},$$

where J values for $E_1(j)$ are given by

$$J\left[A_1(j), B_1(j)/U_{l'}, j\right] = \int_0^{U_{l'}} p(t,0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_{l'}} p(t,1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_{l'}} p(t,j/A_1)Q(t-s, j/B_1)ds$$

$$J\left[A_1(j), B_1(j)/U_{l'-1}, j\right] = \int_0^{U_{l'-1}} p(t,0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_{l'-1}} p(t,1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_{l'-1}} p(t,j/A_1)Q(t-s, j/B_1)ds$$

$$J\left[A_1(j), B_1(j)/U_n, j\right] = \int_0^{U_n} p(t,0/A_1)Q(t-s, j/B_1)ds$$

$$+\int_0^{U_n} p(t,1/A_1)Q(t-s, j/B_1)ds \quad \cdots \quad +\int_0^{U_n} p(t,j/A_1)Q(t-s, j/B_1)ds$$

Suppose $[U_{l-1}, U_l) \subseteq [U_{n-l}, U_{n-m})$, and $E_2 \in [U_{n-l}, U_{n-m})$ then

$$Pr\left[E_2(j)/E(j)\right] = Pr\left[U_{l'-1} \leq J \leq U_{l'}, j/J \leq U_n\right]$$

$$= \frac{J\left[A_2(j), B_2(j)/U_{l'}, j\right] - J\left[A_2(j), B_2(j)/u_{l'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]}$$

where J values for $E_2(j)$ are given as below:

$$
\begin{aligned}
J\left[A_2(j), B_2(j)/U_{l'}, j\right] &= \int_0^{U_{l'}} p(t, 0/A_2) Q(t-s, j/B_2) ds \\
+ \int_0^{U_{l'}} p(t, 1/A_2) Q(t-s, j/B_2) ds \quad \cdots \quad &+ \int_0^{U_{l'}} p(t, j/A_2) Q(t-s, j/B_2) ds \\
J\left[A_2(j), B_2(j)/U_{l'-1}, j\right] &= \int_0^{U_{l'-1}} p(t, 0/A_2) Q(t-s, j/B_2) ds \\
+ \int_0^{U_{l'-1}} p(t, 1/A_2) Q(t-s, j/B_2) ds \quad \cdots \quad &+ \int_0^{U_{l'-1}} p(t, j/A_2) Q(t-s, j/B_2) ds \\
J\left[A_2(j), B_2(j)/U_{n}, j\right] &= \int_0^{U_{n}} p(t, 0/A_2) Q(t-s, j/B_2) ds \\
+ \int_0^{U_{n}} p(t, 1/A_2) Q(t-s, j/B_2) ds \quad \cdots \quad &+ \int_0^{U_{n}} p(t, j/A_2) Q(t-s, j/B_2) ds
\end{aligned}
$$

If $E_1(j) = E_2(j) \in [U_{p'-1}, U_{p'}) \subseteq [U_{n-k}, U_{n-m})$ i.e. $Z_1(j) = Z_2(j)$, then the conditional probabilities contain the same parameter sets. The probabilities for this situation are

$$
\begin{aligned}
Pr\left[E_1(j) = E_2(j)/E(j)\right] &= Pr\left[U_{p'-1} \leq J \leq U_{p'}, j/J \leq U_n\right] \\
&= \frac{J\left[A_2(j), B_2(j)/U_{p'}, j\right] - J\left[A_2(j), B_2(j)/u_{p'-1}, j\right]}{J\left[A_2(j), B_2(j)/U_n, j\right]},
\end{aligned}
$$

where J values for $E_2(j)$ are given by

$$
\begin{aligned}
J\left[A_2(j), B_2(j)/U_{p'}, j\right] &= \int_0^{U_{p'}} p(t, 0/A_2) Q(t-s, j/B_2) ds \\
+ \int_0^{U_{p'}} p(t, 1/A_2) Q(t-s, j/B_2) ds \quad \cdots \quad &+ \int_0^{U_{p'}} p(t, j/A_2) Q(t-s, j/B_2) ds \\
J\left[A_2(j), B_2(j)/U_{p'-1}, j\right] &= \int_0^{U_{p'-1}} p(t, 0/A_2) Q(t-s, j/B_2) ds \\
+ \int_0^{U_{p'-1}} p(t, 1/A_2) Q(t-s, j/B_2) ds \quad \cdots \quad &+ \int_0^{U_{p'-1}} p(t, j/A_2) Q(t-s, j/B_2) ds
\end{aligned}
$$

$$J\left[A_2(j), B_2(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_2)Q(t-s, j/B_2)ds$$
$$+\int_0^{U_n} p(t, 1/A_2)Q(t-s, j/B_2)ds \cdots +\int_0^{U_n} p(t, j/A_2)Q(t-s, j/B_2)ds$$

Since $Z_3(j) > \{Z_0(j), Z_1(j), Z_2(j)\}$, suppose $E_3(j) \in [U_{m'-1}, U_{m'}) \subseteq [U_{n-m}, U_n]$, now above probabilities are

$$Pr\left[E_3(j)/E(j)\right] = Pr\left[U_{m'-1} \leq J \leq U_{m'}, j/J \leq U_n\right]$$
$$= \frac{J\left[A_3(j), B_3(j)/U_{m'}, j\right] - J\left[A_3(j), B_3(j)/u_{m'-1}, j\right]}{J\left[A_3(j), B_3(j)/U_n, j\right]}$$

where J values for $E_3(j)$ are given by

$$J\left[A_3(j), B_3(j)/U_{m'}, j\right] = \int_0^{U_{m'}} p(t, 0/A_3)Q(t-s, j/B_3)ds$$
$$+\int_0^{U_{m'}} p(t, 1/A_3)Q(t-s, j/B_3)ds \cdots +\int_0^{U_{m'}} p(t, j/A_3)Q(t-s, j/B_3)ds$$

$$J\left[A_3(j), B_3(j)/U_{m'-1}, j\right] = \int_0^{U_{m'-1}} p(t, 0/A_3)Q(t-s, j/B_3)ds$$
$$+\int_0^{U_{m'-1}} p(t, 1/A_3)Q(t-s, j/B_3)ds \cdots +\int_0^{U_{m'-1}} p(t, j/A_3)Q(t-s, j/B_3)ds$$

$$J\left[A_3(j), B_3(j)/U_n, j\right] = \int_0^{U_n} p(t, 0/A_3)Q(t-s, j/B_3)ds$$
$$+\int_0^{U_n} p(t, 1/A_3)Q(t-s, j/B_3)ds \cdots +\int_0^{U_n} p(t, j/A_3)Q(t-s, j/B_3)ds$$

Using the above conditional probabilities, likelihood functions are constructed by assuming some parametric form for the diagnosed disease cases. For each age group above, analysis is conducted to estimate the incubation periods by age group.

7. Conclusions

The improved models that address the impacts of anti-retroviral therapy, protease inhibitors and combination of drugs presented in section 1 seem useful in understanding the dynamics of variables for individuals with the full blown disease for no-drug, *drug 1, drug 2* and *drug 3, i.e* $D_{z_0}, D_{z_1}, D_{z_2}$and D_{z_3}. Using the methodology in sections 2 to 4, (despite being lengthy), we are able to estimate the parameters for the incubation period for each drug type, by the deconvolution method. We have demonstrated this method for three types of drugs, and one can obtain $\mathbf{B}$ for as many drugs as possible from the formulae for $n-$types of drugs in section 3. So far, there is no evendence of drugs being useful in avoiding contracting the disease. Drugs may be useful for avoiding opportunistic infections for some specific periods of time. Eventually, an individual will succumb to AIDS, whether or not that individual takes drugs (which is also demonstrated in the truncation effect). The truncation effect formulae can be used to obtain the parameter set (say, $\mathbf{B}^T$), but we did not demonstrate this numerically.

We did not introduce intracellular delay that might arise due drug interventions. There are not many quantititive results available on the relationship between the dose of a drug and the resultant delay in the development of the disease. Suppose $s_1, s_2, s_3..., s_k$ are k levels of doses of a single drug, and $\tau_1, \tau_2, \tau_3, ..., \tau_k$ are the respective delays obtained in producing a new infected cell. Then we can write the relation $R^2(s, \tau)$ between s and τ as

$$\frac{\left\{\sum_{i=1}^{k}(s_i - \overline{s})(\tau_i - \overline{\tau})\right\}^2}{\left\{\sum_{i=1}^{k}(s_i - \overline{s})\right\}^2 \left\{\sum_{i=1}^{k}(\tau_i - \overline{\tau})\right\}^2}$$

$R(s, \tau)$ is called the correlation coefficient of dose-delay. $\overline{s}$ is the mean dose-level and $\overline{\tau}$ is the mean delay. This experiment can be conducted for various doses s_{ij} (say) for drug type $j = 1, 2, 3...n$. Each drug will produce a delay depending upon the dose level. From this, the average delay can be statistically compared to understand the mean dose effect due to a particular drug, and hence the drug efficacy. However, this does not give dynamics over the time period, but it is very useful in preparing the baseline parameters for simulation studies, and also for the models explained in sections 1, 2 and 5. There might be a possibility of exploring the impact of delay in the conditional probabilities expressed in this work.

Our work may be interesting for people working on developing computational techniques for solving integro-differential equations, algorithms to solve convolution type equations in epidemiology, and EM-type algorithms. The

age-structure analysis presented is more complicated than analysis presented for the non-age structured populations, and we provide a new kind of analysis for the incubation period. When reported disease cases and densities of the infection are available for a period of several years in the population, then this kind of analysis offers a reliable method to estimate the incubation period distribution.

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Appendix I : Conditional probabilities for generalized multiple drug impact

Here we derive expressions for conditional probabilities when several drugs are available, and the incubation period is non-monotonic. When such a situation arises there will be several combinations of orders of Zs. We take one such situation and write corresponding Ls for the purpose of demonstration.

Suppose $Z_0 < ... < Z_k = ... = Z_{k+n+1} < ... < Z_N$. Let us divide this into the following two inequalities and an equality: $Z_0 < ... < Z_k$, $Z_{k+1} = ... = Z_{k+n}$ and $Z_{k+n+1} < ... < Z_N$. If we consider the first and third inequalities, then

$$\begin{aligned}\mathcal{D}\left(\mathbf{A},\mathbf{B}/U_{N_k}\right) &= \int_0^{U_{N_0}} h(t/A_{N_0})G(t-s/B_{N_0})ds + \\ &\int_{U_{N_0}}^{U_{N_1}} h(t/A_{N_1})G(t-s/B_{N_1})ds \\ &\cdots + \int_{U_{N_{k-1}}}^{U_{N_k}} h(t/A_{N_k})G(t-s/B_{N_k})ds\end{aligned}$$

$$\begin{aligned}\mathcal{D}\left(\mathbf{A},\mathbf{B}/U_{N_N}\right) &= \int_0^{U_{N_{n+k+1}}} h(t/A_{N_{n+k+1}})G(t-s/B_{N_{n+k+1}})ds + \\ &\int_{U_{N_0}}^{U_{N_{n+k+2}}} h(t/A_{N_{n+k+2}})G(t-s/B_{N_{n+k+2}})ds \\ &\cdots + \int_{U_{N_{N-1}}}^{U_{N_N}} h(t/A_{N_N})G(t-s/B_{N_N})ds\end{aligned}$$

We can express $\{P\left(E_{N_\theta}/E\right)\}_{\theta=0}^{\theta=k}$ and $\{P\left(E_{N_\theta}/E\right)\}_{\theta=n+k+1}^{\theta=N}$ and the corresponding $\{L_{N_\theta}\}_\theta$ as shown in the section 3. Then L_{N_θ} is maximised for the set $[A_\theta, B_\theta]$. We obtain $N-n-k$ sets of $[\mathbf{A},\mathbf{B}]$ values, and the corresponding likelihood functions $\{L_{N_\theta}\}_{\theta=0}^{k}$ and $\{L_{N_\theta}\}_{\theta=n+k+1}^{N}$

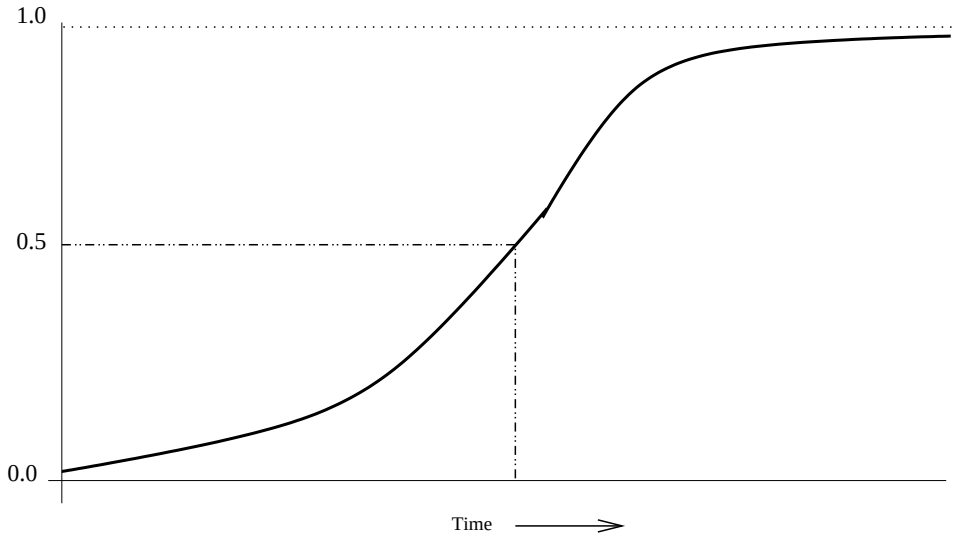

FIGURE 7.1. Truncated incubation period. The idea of truncated cumulative distribution of the incubation period is plotted. After a certain time duration, there will not be any gain due to therapy. Median incubation period is represented by the line cutting the curve at 0.5, corresponding to the Y-axis.

Appendix II: Truncated incubation period

Suppose there is an upper bound for the impact of drugs on the incubation period; that is, the incubation period cannot be increased after a certain time point after the drug use. Then the likelihood equations explained in section 4 would change accordingly. There was an attempt earlier to truncate the incubation period with the help of the truncated Weibull distribution (Rao and Kakehashi, 2005). They have not seen the impact of drugs using such functions. If Z, the length of the incubation period, and if Z_c is the truncation point, then $G(Z) = 1 - \exp\left\{-\left(\frac{z}{\delta_1}\right)^{\delta_2}\right\}$, for $0 < Z < Z_c$, and $G(\mathcal{Z}) = 1 - \exp\left\{-\left(\frac{z}{\delta_1}\right)^{\delta_2}\right\} \exp\left\{-\left(\frac{\delta_2}{\delta_1}\right)\left(\frac{t_c}{\delta_1}\right)^{(\delta_2-1)(z-z_c)}\right\}$, for $Z \geq Z_c$. Here, δ_1, δ_2 are scale and shape parameters. One can construct a likelihood function for each drug type using such functions as follows:

$$L(\mathbf{A}, \mathbf{B}/P_j) = L_{<Z_c} + L_{\geq Z_c}, \tag{7.1}$$

where

$$
\begin{aligned}
L_{<Z_c} &= \prod_j b_1(j)b_2(j) - \prod_j b_1(j-1)b_2(j) \\
L_{\geq Z_c} &= \prod_j b_1^t(j)b_2^t(j) - \prod_j b_1^t(j-1)b_2^t(j)
\end{aligned}
$$

and

$$
\begin{aligned}
b_1(j) &= \left\{ \int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1} \right)^{\delta_2} \right\} \right\} ds \right\}^{T_j} \\
b_1(j-1) &= \left\{ \int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1} \right)^{\delta_2} \right\} \right\} ds \right\}^{T_j} \\
b_2(j) &= \left\{ \int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} \left\{ 1 - \exp\left\{ -\left(\frac{t}{\delta_1} \right)^{\delta_2} \right\} \right\} ds \right\}^{-T_j} \\
b_1^t(j) &= \left[\int_0^{u_j} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1} \right)^{\delta_2} \right\} \times \right. \\
&\qquad \left. \exp\left\{ -\left(\frac{\delta_2}{\delta_1} \right) \left(\frac{t_c}{\delta_1} \right)^{(\delta_2 - 1)(z - z_c)} \right\} ds \right]^{T_j} \\
b_1^t(j-1) &= \left[\int_0^{u_{j-1}} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1} \right)^{\delta_2} \right\} \times \right. \\
&\qquad \left. \exp\left\{ -\left(\frac{\delta_2}{\delta_1} \right) \left(\frac{t_c}{\delta_1} \right)^{(\delta_2 - 1)(z - z_c)} \right\} ds \right]^{T_j} \\
b_2^t(j) &= \left[\int_0^{u_n} e^{\alpha_1 s^2 + \alpha_2 s + \alpha_3} 1 - \exp\left\{ -\left(\frac{z}{\delta_1} \right)^{\delta_2} \right\} \times \right. \\
&\qquad \left. \exp\left\{ -\left(\frac{\delta_2}{\delta_1} \right) \left(\frac{t_c}{\delta_1} \right)^{(\delta_2 - 1)(z - z_c)} \right\} ds \right]^{-T_j} .
\end{aligned}
$$

For each drug type, an expression of the type 7.1 can be derived. Despite the assumption on truncation as mentioned above, the incubation period could vary according to the type of the drug.